

Contrary to the Examiner's assertion, M.P.E.P. § 803.04 explains that the partial waiver of the requirements of 37 C.F.R. § 1.141 is to be applied to up to ten different SEQ ID NOs. Specifically, M.P.E.P. § 803.04 states

Examples of typical nucleotide sequence claims impacted by the partial waiver of 37 CFR 1.141 *et seq.* . . . include

(A) an isolated and purified DNA fragment comprising DNA having at least 95% identity to a DNA sequence selected from SEQ ID Nos. 1-1,000; . . .

Applications claiming more than ten individual independent and distinct nucleotide sequences in alternative form, such as set forth in example (A), will be subject to a restriction requirement. Only the ten nucleotide sequences selected in response to the restriction requirement and any other claimed sequences which are patentably indistinct therefrom will be examined.

M.P.E.P. § 803.04.

Thus, contrary to the Examiner's assertion, the M.P.E.P. does not state that the requirements apply to fragments of one single SEQ ID NO, but rather *fragments of up to 10 different SEQ ID NOs*. Rejoinder of claim 79 would only involve examination of two sequences. Accordingly, Applicants request rejoinder of claim 79.

#### ***Utility rejection***

The Examiner maintained the rejection of claims 23, 29, 35, 41, 49, 55, 63 and 69 under 35 U.S.C. § 101 for alleged lack of utility. Applicants respectfully traverse this rejection.

The Examiner stated that "[t]here is no evidence in the specification nor any art of record to document that SEQ ID NO:1 is translated into a peptide which is expressed or overexpressed in malignant breast tissue." Paper No. 17, page 3.

Applicants submit herewith as Exhibit A Jia *et al.*, *Cancer Res.* 59:742-747 (1999). Jia *et al.* showed that expression of BCSG1 protein (also termed  $\gamma$ -synuclein) stimulated the invasiveness and migration of a murine cell line, MDA-MB-435 *in vitro*. Jia *et al.* also show that BCSG1 protein stimulates the metastasis of MDA-MB-435 tumors *in vivo*. This confirms that the BCSG1 protein is a factor in breast cancer metastasis.

The Examiner further stated that "[t]he specification gives only general suggestions regarding the production of antibodies which could be applied to many different proteins and peptides. Thus the asserted utility for hypothetical SEQ ID NO:2 is a general utility, not specific to SEQ ID NO:1." Paper No.17, page 3.

Applicants assert that the use of BCSG1 to raise antibodies is specific. While the methods regarding the production of antibodies which are given in the specification can be applied to many different proteins, only BSCG1 polypeptides may be used to raise antibodies which are specific for BSCG1. The antibodies raised by the polypeptides of the invention are themselves useful in breast cancer prognosis. This is not a general utility, as most proteins cannot be used to raise antibodies for breast cancer prognosis.

Applicants assert that the use of BCSG1 polypeptides to raise antibodies useful for breast cancer prognosis is specific, substantial, and credible. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner also maintained the rejection of claims 23, 29, 35, 41, 49, 55, 63 and 69 under 35 U.S.C. § 112 for alleged lack of utility. For the reasons discussed above in

response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a specific utility. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV) at 2100-28 (Rev.1, Feb. 2000). Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

***Enablement rejection***

The Examiner rejected claims 16, 18, 20-22, 24-28, 30-34, 36-40, 42-48, 50-54, 56-62, 64-68 and 70-78 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse this rejection.

*(A) Polynucleotides encoding the complete amino acid sequence encoded by the cDNA of the ATCC clone 97856 or SEQ ID NO:2 or fragments thereof*

(c) h  
The Examiner stated that "[t]he specification has not demonstrated that the protein of SEQ ID NO:2 is translated . . . nor has it taught a specific use of the hypothetical SEQ ID NO:2, and further, the specification does not teach a polynucleotide which encodes a large fragment of SEQ ID NO:2 which further comprises a heterologous polynucleotide." Paper No. 17, page 4.

The specification, at page 8, line 29 to page 9, line 7, describes the particular fragments recited in claim 57. The specification, at page 10, lines 6-27, also teaches that the polynucleotides of the invention (including those which are fragments of a polynucleotide encoding SEQ ID NO:2) may include heterologous sequences, including leader sequences,

non-coding sequences, marker sequences, and Fc. Thus, the specification does in fact teach a polynucleotide which encodes a fragment of SEQ ID NO:2 which further comprises a heterologous polynucleotide.

As stated above in reference to the utility rejection, it has been shown that the BCSG1 protein is involved in breast cancer metastasis. Applicants assert that it is not necessary to enable a use of the protein for these claims, as they are directed to polynucleotides. The polynucleotides are useful as probes or primers in the prognosis of breast cancer.

Nevertheless, the polynucleotides of the invention are also useful for producing polypeptides which raise antibodies for detecting metastatic breast cancer. Page 24, lines 22-27 describes the regions of the BCSG1 polypeptide which may be used to generate BCSG1 specific antibodies. Page 29, lines 16-24 describe antibody-based methods for assaying BCSG1 protein levels. One of ordinary skill in the art, from this disclosure, would be able to use the polynucleotides of the invention, for breast cancer diagnosis and for the production of breast cancer-specific antibodies.

*(B) Polynucleotides comprising fragment of SEQ ID NO:1*

The Examiner stated that "[t]he specification does not teach a use for polypeptides [sic] comprising 50, 100 or 250 contiguous nucleotides of SEQ ID NO:1 which further comprise heterologous polynucleotides, since the specification puts forth only full-length SEQ ID NO:1 as a probe." Paper No. 17, page 5.

Contrary to the Examiner's assertion, the specification does indeed teach that shorter fragments of SEQ ID NO:1 are useful as probes or primers. *See* specification, page 8, line

20. Thus, all polynucleotides encompassed by these claims are useful as probes or primers to detect breast cancer. One of ordinary skill in the art would know how to use the polynucleotides of the invention based on the disclosure provided. Thus, claims directed to polynucleotides comprising fragments of SEQ ID NO:1 are enabled.

*C) Polynucleotides 95% identical to polynucleotides encoding SEQ ID NO:2 and polynucleotides encoding variants of SEQ ID NO:2.*

The Examiner stated that "[c]laims 71 and 76 are drawn to polynucleotides which are 95% identical to the polynucleotides which encode SEQ ID NO:2." Paper No. 17, page 5.

Contrary to the Examiner's assertion, and as explained below, claim 76 is not drawn to a polynucleotide which is 95% identical to polynucleotides encoding SEQ ID NO:2. Rather, claim 76 is drawn to a polynucleotide *encoding an amino acid sequence 95% identical to SEQ ID NO:2.*

The Examiner stated that

[t]he specification fails to give any guidance on the correlation between the amino acid sequence and the function of the protein, therefore one of skill in the art would not know how to modify the amino acid sequence without adversely affecting the function of the hypothetical protein. . . given the lack of guidance in the specification for choosing which amino acids to exchange, either separately or in groups, and which specific amino acids can be substituted in at any specified location, one of skill in the art would not know how to make or use the instant invention.

Paper No. 17, page 7.

Each of the polynucleotides of the claims are useful as probes to detect breast cancer.

Thus, it is not necessary to determine which amino acids can be substituted to obtain a protein with BCSG1 activity.

Nevertheless, Applicants have provided in the specification, at page 9, lines 3-4, those regions of BCSG1 which are useful for raising antibodies for breast cancer diagnosis. One of ordinary skill in the art would know not to substitute these regions of BCSG1 in order to obtain an antigenic polypeptide. These variants of SEQ ID NO:2 can then be used to raise breast cancer diagnostic antibodies. Thus, one of ordinary skill would be enabled to make and use the polynucleotides of the invention.

*D) Polynucleotide variants of SEQ ID NO:1 and polynucleotides which hybridize to SEQ ID NO:1*

The Examiner stated that

[c]laims 77 and 78 are drawn to polynucleotides which are 95% identical to SEQ ID NO:1 and polynucleotides which hybridize under stringent conditions to SEQ ID NO:1. Neither term is limiting with respect to the function of the claimed polynucleotides. . . The specification fails to provide an enabling disclosure for how one would use such polynucleotides.

Paper no. 17, page 7.

Each of the polynucleotides falling within claims 77 and/or 78 are useful as probes to detect breast cancer. *See* specification, page 9, lines 21-22; page 12, line 26 to page 13, line 7; and page 28, lines 5-10. Claim 77 is drawn to polynucleotides which are 95% identical to SEQ ID NO:1; due to their high level of homology, each of these polynucleotides would hybridize to SEQ ID NO:1. One of the limitations of claim 78 is that the polynucleotides hybridize to SEQ ID NO:1. All of the polynucleotides falling within the claims can be used to detect breast cancer, as each of them will hybridize with the BCSG-1 native polynucleotide. Thus, it is not necessary to provide a further function of the claimed

polynucleotides, since Applicants have enabled one use of all the polynucleotides of the claims.

Applicants have addressed all the Examiner's grounds of rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Accordingly, withdrawal of this rejection is respectfully requested.

***Indefiniteness rejection***

The Examiner rejected claim 71 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner states that the claim is unclear for the recitation of "a first nucleic acid", as "[i]t is unclear what the applicant intends the second nucleic acid to be." Paper no. 17, page 7. Applicants have amended claim 71 to no longer recite "first nucleic acid." Accordingly, withdrawal of this rejection is respectfully requested.

***Other Matters***

The Examiner stated that "[c]laims 71 and 76 appear to claim the same invention." Paper No. 17, page 8. Claims 71 and 76 are of differing scope. Claim 71 is directed to isolated polynucleotides which are 95% or more identical to nucleotides encoding particular amino acid sequences. Claim 76 is directed to isolated polynucleotides encoding an amino acid sequence 95% or more identical to particular amino acid sequences. Since one claim is directed to polynucleotides 95% or more identical to other nucleotides, and the other claim is directed to polynucleotides encoding amino acid sequences 95% or more identical to other amino acid sequences, the scope of the claims differ.

***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: February 22, 2001

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